A Review of Vitamin B12 in Dermatology

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REVIEW ARTICLE

A Review of Vitamin B12 in Dermatology

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Abstract Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is important in the hematological and nervous systems, and it has a complex relationship with the skin. Altered cobalamin levels can lead to dermatological manifestations, which may indicate a deficiency or excess of this vitamin. The biochemistry and metabolism of cobalamin is complex, and diseases can be associated with alterations of this metabolic pathway. The cutaneous manifestations of cobalamin deficiency include hyperpigmentation (most commonly); hair and nail changes; and oral changes, including glossitis. Additionally, several dermatologic conditions, including vitiligo, aphthous stomatitis, atopic dermatitis, and acne are related to cobalamin excess or deficiency. The cutaneous complications of cobalamin therapy include acne, rosacea, and allergic site reactions, or anaphylaxis with cobalamin injections. As cobalt is a component of cobalamin, patients with cobalt sensitivity have been reported to have cutaneous manifestations when receiving cobalamin replacement therapy.

Key Points

Cobalamin deficiency and excess is important to consider in the differential diagnosis of hyperpigmentation (especially with accentuation in flexural areas, palms, soles, and the oral cavity), glossitis, vitiligo, atopic dermatitis, erythema nodosum, and hair and nail changes.

The dermatological complications of cobalamin therapy include, but are not limited to, acneiform eruptions, rosacea, allergic dermatitis, and anaphylaxis.

Isotretinoin can decrease cobalamin levels, while atopic dermatitis and aphthous stomatitis can be treated with different formulations of cobalamin. Current research regarding cobalamin therapy for vitiligo is inconclusive.

1 Introduction

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is very important in the hematological and nervous systems. It exists in many forms in the body, and is a cofactor for homocysteine methyltransferase and methylmalonyl-CoA mutase. The primary source for cobalamin is animal products, as it is synthesized by microorganisms such as bacteria. This paper reviews the metabolism of cobalamin, diseases associated with an elevated cobalamin level, the clinical manifestations of cobalamin deficiency, several dermatologic conditions (vitiligo, aphthous

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stomatitis, atopic dermatitis) and their relationships to cobalamin, and complications of cobalamin therapy. The focus is on the disease states and findings that are significant to the dermatologist, in an effort to increase awareness of the various manners in which cobalamin alterations can influence the diagnosis and treatment of several diseases.

2 Biochemistry of Cobalamin

Vitamin B12 exists in many forms in the body, two of which are biologically active coenzymes: methylcobalamin and adenosylcobalamin. Methylcobalamin is a coenzyme with methionine synthase, a key enzyme in the folic acid-dependent synthesis of pyrimidines and purines. Adenosylcobalamin is involved in the enzymatic degradation of fatty acids by methylmalonyl CoA mutase. These enzymes are needed for normal function of bone marrow and the central nervous system [1].

Cobalamin has a complex uptake and metabolism that requires several coenzymes (Fig. 1). When cobalamin is ingested from food sources, it is first released from the proteins in food by pepsin in the stomach. It then binds to haptocorrin, which is found in saliva and protects cobalamin from the acidic environment of the stomach. Haptocorrin is then degraded in the duodenum by digestive proteases and the free cobalamin binds to intrinsic factor. Intrinsic factor is needed for cobalamin to be absorbed by receptors on the enterocytes in the terminal ileum and to protect it from catabolism by intestinal bacteria. Cobalamin is then transported into the portal circulation and taken up by the liver. The majority of cobalamin in circulation is bound to haptocorrin, with a smaller percentage bound to transcobalamin II, and a negligible amount of circulating free cobalamin [2]. It is taken up into tissues, mainly the liver, via transcobalamin receptors, which are located on endothelial cells and not hepatocytes themselves. The liver stores enough cobalamin to last several years before symptoms of deficiency present [3].

Due to the complexity of the metabolism and absorption of cobalamin, there are many opportunities for defects to occur, which can result in deficiency or imbalance.

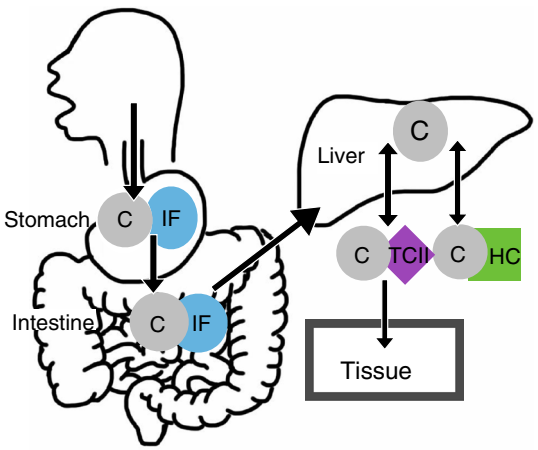

Fig. 1 Cobalamin's complex metabolism: after cobalamin is ingested and goes to the stomach, it is released from proteins in food by pepsin and then binds to haptocorrin, which protects it from the acidic stomach environment. In the duodenum, haptocorrin is degraded by digestive proteases, and free cobalamin binds to intrinsic factor, which helps the absorption of cobalamin by receptors on enterocytes in the terminal ileum. It is then taken up into the portal circulation and absorbed by the liver via transcobalamin receptors on endothelial cells. *C* cobalamin, *H* haptocorrin, *IF* intrinsic factor, *TCII* transcobalamin

3 Elevated Cobalamin Levels

Elevated cobalamin levels are defined as serum levels above 950 pg/ml (701 pmol/L) and can be caused by excess intake or administration (e.g. with cobalamin therapy), liberation from an internal reservoir, and commonly from a qualitative or quantitative increase in transcobalamin (transporter of cobalamin) from excess production or a lack of clearance, as well as a lack of affinity for transcobalamin to cobalamin [4]. Elevated cobalamin is seen in several pathologic states, including chronic myelogenous leukemia, promyelocytic leukemia, polycythemia vera, and hypereosinophilic syndrome. Of these conditions, the greatest elevation of cobalamin is seen in hypereosinophilic syndrome. The increased cobalamin level is caused by increased production of haptocorrin by granulocytes and their precursors. Haptocorrin can be a useful tool in differentiating primary and secondary eosinophilia, as it is not associated with secondary eosinophilia, as seen with parasitic infections [2]. In hypereosinophilic syndrome, elevated cobalamin levels in combination with elevated tryptase levels can identify a subset of patients with a myeloproliferative variant of the disease with tissue fibrosis and poor prognosis. These patients harbor the FIP1L1-PDGFRA mutation, which confers responsiveness to imatinib [5]. In addition to myeloproliferative disorders, acute hepatitis, cirrhosis, hepatocellular carcinoma, and metastatic liver disease can show an increase in circulating cobalamin, caused by cobalamin release during hepatic cytolysis and/or decreased cobalamin clearance by the affected liver [2]. Many of the disease processes that have elevated cobalamin levels can also have skin findings. For example, hypereosinophilic syndrome can manifest as eczema, erythroderma, lichenification, recurrent urticaria, angioedema, and less commonly in difficult-to-treat mucosal ulcers [6]. Additionally, elevated cobalamin levels from cobalamin therapy can result in cutaneous manifestations and are discussed later.

4 Cobalamin Deficiency

Vitamin B12 is one of the most common vitamin deficiencies, yet there is no consensus for a cut-off point for cobalamin or for folate, holotranscobalamin, methylmalonic acid, and homocysteine. A recent review article showed that serum cut-off points for deficiency in journal articles widely ranged: for cobalamin 100–350 pmol/L, holotranscobalamin 20–50 pmol/L, methylmalonic acid 0.210–0.470 μmol/L, homocysteine 10–21.6 μmol/L, and folate 3.7–15.9 nmol/L [7]. Additionally, cobalamin pseudo-deficiency (low cobalamin serum levels but no true deficiency) can rarely be caused by a transcobalamin deficiency. In this case, determining levels of methylmalonic acid and homocysteine would reveal this pseudo-deficiency, and treatment with cobalamin therapy would be unnecessary [8]. Another way to test for cobalamin deficiency is by measuring methylmalonic acid in the urine, which has been shown to be a reliable laboratory marker in newborns [9].

Findings of decreased serum cobalamin, elevated methylmalonic acid or elevated homocysteine can be used to make a diagnosis of vitamin B12 deficiency (Fig. 2). One study of 406 patients with known vitamin B12 deficiency showed that 98.4 % of patients had elevated serum methylmalonic acid levels and 95.9 % had elevated serum homocysteine levels (defined as three standard deviations above the mean). When both methylmalonic acid and homocysteine levels are used for diagnosis, there is a sensitivity of 99.8 %. In this study, 28 % of the patients had normal hematocrit levels and 17 % had normal mean corpuscular volumes, thus hematological manifestations of the cobalamin deficiency were not yet observed [10]. When evaluating laboratory values, one must also consider that folate deficiency can elevate homocysteine and falsely lower serum vitamin B12 levels. Additionally, renal disease can elevate methylmalonic acid.

The prevalence of cobalamin deficiency is difficult to assess since under-diagnosis is likely and subclinical disease is considered common. Cobalamin deficiency is rarely

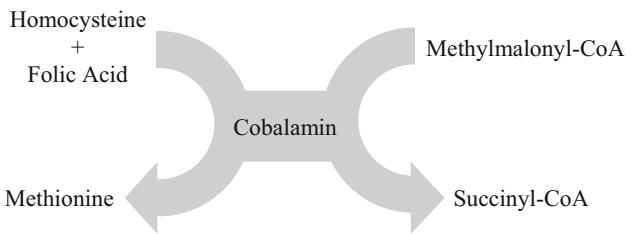

Fig. 2 Cobalamin is a co-factor for the enzymes homocysteine methyltransferase and methylmalonyl-CoA mutase. This facilitates the conversion of homocysteine, folic acid, and methylmalonyl-CoA to methionine and succinyl-CoA. *CoA* coenzyme A

due to inadequate intake, although it can occasionally be seen in strict veganism. It is typically a result of malabsorption (from sprue, enteritis, or infection with *Diphyllobothrium latum*), pernicious anemia (with a decrease in gastric intrinsic factor), surgical resection of the terminal ileum (often with Crohn's disease), or overgrowth of intestinal bacteria. It can also be seen in infants from a mother with vitamin B12 deficiency, which can lead to failure to thrive and other developmental problems [1]. A very common cause of cobalamin deficiency is the widespread use of gastric acid-blocking agents, especially in the aging population [11].

The normal variation in cobalamin and folate levels has been tied to various genetic loci in different populations. The gene products are involved in the pathways of cobalamin uptake and metabolism [12]. Genetic defects in the intracellular processing of cobalamin have been classified into nine complementation groups. These mutations result in methylmalonic aciduria, homocystinuria, or a combination of the two, with devastating results. Currently, there is widespread newborn screening for homocysteine and methylmalonate, highlighting the importance of identifying and treating these patients early [13]. The most recently described mutation involves the adenosine triphosphate (ATP)-binding cassette transporter ABCD4, which is involved in the release of cobalamin from lysosomes into the cytoplasm [14]. While the other mutations result in severe phenotypes with little appreciable skin findings, this mutation has been reported to produce a phenotype of skin pigmentation. In one case, a 14-year-old boy presented with hyperpigmentation alongside neurologic abnormalities [15], while another case demonstrated diffuse progressive skin pigmentation in the absence of neurological or cardiovascular complications in a 12-year-old girl [16].

A very rare cause of cobalamin deficiency is the recreational abuse of nitric oxide gas. In one case report, a patient presented with skin hyperpigmentation after abusing nitrous oxide for 2 years, and was found to also have myeloneuropathy of the posterior and lateral columns, a low serum vitamin B12 level, and an elevated serum homocysteine level [17].

Extracutaneous clinical manifestations of cobalamin deficiency vary widely. Hematological manifestations include megaloblastic macrocytic anemia with hypersegmented polymorphonuclear cells and pancytopenia. Neurological findings may include paresthesias, peripheral neuropathy, and combined systems disease with demyelination of dorsal columns and corticospinal tract. Psychiatric changes include irritability, personality change, mild memory impairment, dementia, depression, and psychosis. There have been numerous reports of cobalamin deficiency presenting with delusions of parasitosis, so an evaluation of the serum cobalamin and folate should be considered [18].

Other manifestations include a possible increased risk of myocardial infarction and stroke as well as infertility [11]. Some of these manifestations can be attributed to the elevated levels of homocysteine and methylmalonic acid seen with cobalamin deficiency.

5 Cutaneous Manifestations of Cobalamin Deficiency

There are various cutaneous findings associated with cobalamin deficiency, the majority of which are more prevalent in patients with darker pigmentation. A retrospective and prospective study of 63 individuals with vitamin B12 deficiency-related neurological syndromes in India showed that 41 % had skin and mucosal changes, with glossitis in 31 %, hyperpigmentation in 19 %, hair changes in 9 %, angular stomatitis in 8 %, and vitiligo in 3 % [19]. Additionally, a case report described erythema nodosum as a presenting sign of cobalamin deficiency in a 38-year-old female, where the erythema nodosum resolved with replacement of vitamin B12 [20].

The pattern of hyperpigmentation is generalized with accentuation in flexural areas, palms, soles, and the oral cavity. It may also be accentuated in areas of pressure, such as the terminal phalanges, knees, and elbows. Hyperpigmentation may be the first manifestation of vitamin B12 deficiency [21]. Additionally, you can see linear streaks on the nails and hair changes including poliosis [22]. These findings tend to reverse over months with replacement therapy.

The pathologic diagnosis of hyperpigmentation from vitamin B12 deficiency shows increased melanin in the basal layer of the epidermis. One electron microscopic study showed many melanosomes in melanocytes and surrounding keratinocytes. This study proposed that the dominant mechanism of hyperpigmentation due to vitamin B12 deficiency is an increase in melanin synthesis [23]. In one patient with a reddish hyperpigmentation due to chronic cobalamin deficiency that resolved with vitamin B12 injections, biopsy demonstrated an increased number of dermal blood vessels. The pathology showed weak expression of vascular endothelial growth factor, which may have promoted the angiogenesis in this patient and could represent a mechanism for the hyperpigmentation from cobalamin deficiency [24]. It has also been speculated that the increase in melanin could be due to the influence of cobalamin decreasing the level of reduced-type glutathione, which normally inhibits tyrosinase [16].

Oral manifestations of cobalamin deficiency include glossitis, glossodynia, recurrent ulcers, lingual paresthesia, distortion of taste (dysgeusia), intolerance of dental prostheses, xerostomia, stomatitis, and cheilitis. Hunter's glossitis (or Moeller–Hunter) is the classic form of vitamin B12-related glossitis, with diffuse erythema and lingual atrophy found in up to 25 % of cases of cobalamin deficiency with oral manifestations. It has been proposed that a more specific and early finding of cobalamin deficiency is glossitis with atrophic linear lesions appearing on the tongue and hard palate. The linear lesions can manifest before anemia develops, making it a useful early diagnostic sign [25].

6 Dermatologic Disease Associations with Cobalamin Deficiency

6.1 Vitiligo

Vitiligo can be a manifestation of cobalamin deficiency, but the two are not associated in a majority of cases of either disease. This makes it difficult to determine when cobalamin deficiency should be investigated in patients presenting with vitiligo. Karadag et al. [26] compared various serum markers of cobalamin deficiency, including cobalamin, folic acid, homocysteine, and holotranscobalamin in a group of 69 patients with vitiligo and 52 individuals in the control group. They found that the vitiligo group had higher homocysteine and hemoglobin levels and lower levels of vitamin B12 and holotranscobalamin, which is considered the earliest marker of deficiency. Their group suggested the association may be due to a common genetic background among patients with cobalamin deficiency, hyperhomocysteinemia, and vitiligo. Two previous studies had investigated the association of elevated homocysteine levels and vitiligo, with conflicting results. Shaker and El-Tahlawi [27] showed that homocysteine levels were significantly higher in 26 patients with vitiligo than in healthy controls, while Balci et al. [28] found no significant difference in the levels of homocysteine between 48 patients with vitiligo and the control group. Similarly, cobalamin as a therapy for vitiligo has yielded contradictory results in the literature. In a study of 15 patients with vitiligo, eight of the patients experienced repigmentation with prolonged oral folic acid and ascorbic acid and parenteral vitamin B12 supplementation [29]. However, another study of 27 patients compared ultraviolet (UV)-B therapy alone and UVB therapy with vitamin B12 and folic acid, and found no significant difference in the repigmentation rates between the two groups [30]. While there may be a relationship between cobalamin deficiency and vitiligo, further research is needed to elucidate the nature of the association and the clinical application.

6.2 Aphthous Stomatitis

Recurrent aphthous stomatitis can be a chronic and debilitating disease refractory to many therapies. Atrophic

glossitis is a well-known manifestation of cobalamin deficiency, but aphthous stomatitis also appears to be related to cobalamin deficiency. Patients with recurrent minor aphthous stomatitis were found to have reduced dietary intake of cobalamin and folate by energy-adjusted nutrient density when compared with age- and gender-matched subjects. No difference was noted when examining vitamin E, vitamin B6, niacin, thiamin, vitamin C, or vitamin A [31]. In a randomized, double-blind, placebo-controlled trial, a 1,000 mcg dose of sublingual vitamin B12 was an effective therapy for the treatment of recurrent aphthous stomatitis regardless of the patients' serum vitamin B12 level [32].

6.3 Acne Treated with Isotretinoin

Karadag et al. [33] studied 68 patients with acne vulgaris and found that isotretinoin therapy reduced their vitamin B12, folic acid, and holotranscobalamin levels while elevating their homocysteine. It was suggested that this cobalamin deficiency may account for the neuropsychiatric side effects of isotretinoin treatment.

6.4 Atopic Dermatitis

Cobalamin has been used as treatment for many dermatological diseases, even when no clinical or subclinical deficiency exists [34]. Topical cobalamin has shown promise as a safe treatment for atopic dermatitis. A randomized, controlled study involving 49 patients with atopic dermatitis tested 0.07 % cyanocobalamin cream for 8 weeks on one side of the body and vehicle on the other side. The cyanocobalamin cream was well tolerated and seemed to work well from the perspective of both the patient and the investigators. The modified Six Area Six Sign Atopic Dermatitis score was used; this measures dryness/desquamation, itching, erosion, lichenification, erythema, and infiltration. In this study, the score dropped to a significantly greater extent on the treated side than on the placebo side (55.34 for the vitamin B12 cream vs. 28.87 for the placebo) [35]. In vitro, vitamin B12 was able to suppress the cytokine production of T lymphocytes, which may initiate the inflammatory events of atopic dermatitis [36]. This may explain why the vitamin B12 cream was a successful treatment. Another study showed that a preparation of a liposomal hydrogel of adenosylcobalamin (a vitamin B12 derivative) had enhanced skin permeability and was more of benefit than cobalamin itself in the treatment of atopic dermatitis in mice [37]. These results provide hope that cobalamin may provide another therapeutic option in the treatment of atopic dermatitis in the future.

7 Complications of Vitamin B12 Therapy

While cobalamin demonstrates promise in the treatment of certain dermatologic conditions, it is already in widespread use to treat cobalamin deficiency. It is important for the dermatologist to recognize various dermatologic adverse effects that can complicate therapy with cobalamin. There have been several reports of monomorphic acneiform eruptions in patients treated with intramuscular cobalamin injections. The eruptions resolved after cessation of the therapy [38]. Cyanocobalamin, pyridoxine (B6), and riboflavin (B2) have been reported to exacerbate existing acne [38]. Supra-therapeutic doses of oral vitamin B12 and B6 at 4,000 and 2,000 % the recommended daily allowance, respectively, resulted in the onset of rosacea fulminans in a 17-year-old female [39]. Allergic and anaphylactic reactions have also been reported in association with intramuscular as well as parenteral cobalamin. These are more common with cyanocobalamin, but have occurred with both of the available formulations, cyanocobalamin and hydroxycobalamin, with some patients showing cross-reactivity to both [40, 41]. In patients only sensitized to cyanocobalamin, changing to hydroxycobalamin is an acceptable treatment [42]. In one case of a patient sensitized to both formulations, Kartal et al. [43] were able to desensitize the patient to cyanocobalamin.

Since cobalt is a component of cobalamin, sensitivity to cobalt may cause problems in patients receiving vitamin B12 replacement therapy. In patients with allergic contact dermatitis to cobalt undergoing oral cobalamin replacement, several cutaneous reactions have been reported, including chronic vesicular hand dermatitis, cheilitis, and stomatitis [44]. Erythematous, pruritic injection site reactions can occur with vitamin B12 injections. Foods naturally containing cobalt in the form of cobalamin have not been associated with systemic contact dermatitis due to the very small amount of cobalt. However, foods containing high amounts of cobalt in other forms have been shown to flare dyshidrotic eczema in some patients, regardless of patch test results [45]. Stuckertand Nedorost proposed a point-based system for patients to reduce their intake of dietary cobalt [46]. Of note, the amount of cobalt in dental implants is increasing and can cause oral hypersensitivity manifesting as a severe burning sensation in the mouth [47]. Cobalt sensitivity is often associated with nickel sensitivity, and asking about nickel allergies may be helpful before starting vitamin B12 therapy [48]. Spot tests for detecting cobalt are commercially available and are important in assessing skin exposure and health risks associated with metal exposures (e.g. http://www.smartpractice.com) [49].

8 Conclusion

Cobalamin is an important vitamin for the proper function of the human body, and deficiency is fairly prevalent with advanced age. The dermatologist can play a role in the diagnosis of deficiency by recognizing its mucocutaneous manifestations. It is also important to recognize cutaneous complications of cobalamin therapy, since many patients are undergoing therapy. Associations exist between cobalamin and dermatologic diseases such as vitiligo, atopic dermatitis, and aphthous stomatitis. Further elucidation of the exact interplay between these diseases and cobalamin may lead to advances in diagnosis and treatment.

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